

PATENT ABSTRACTS OF JAPAN

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(21)Application number : 09-334142 (71)Applicant : TEIJIN LTD
(22)Date of filing : 04.12.1997 (72)Inventor : MAKINO YUJI
KINOSHITA WATARU

(54) POWDERY MEDICINAL COMPOSITION FOR INHALATION

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain the subject composition with favorable deposition onto the trachea, bronchial tube and lung by including medicinal fine particles formed to specific sphericity and a vehicle so as to optimize the mutual agglomeration of the medicinal fine particles and the adhesion between the medicinal fine particles and the vehicle.

SOLUTION: This powder medicinal composition is obtained by including (A) medicinal fine particles formed to such a sphericity as to be ≥ 0.90 as a result of particle evaluation based on Wadell sphericity ψ , having a size of pref. 0.5-10 μm [wherein, the medicinal being highly lipophilic one, such as a adrenal cortical hormone(e.g. beclometasone propionate), sex hormone (e.g. testosterone), activated vitamin D3, prostaglandin] and (B) a vehicle for common inhalants (e.g. lactose) (pref. ≥ 95 wt.% thereof having a particle size of 30-150 μm), in the weight ratio A/B of pref. (0.1:99.9) to (50:50).

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CLAIMS

[Claim(s)]

[Claim 1] The medical-supplies constituent for powdered inhalation which changes including the medicine particle and excipient which were cast by 0.90 or more degrees of sphericity.

[Claim 2] The medical-supplies constituent for powdered inhalation according to claim 1 whose medicine is a lipophilicity medicine.

[Claim 3] The medical-supplies constituent for powdered inhalation according to claim 2 which is one sort chosen from the group which a lipophilicity medicine becomes from adenocoriticotropic hormone, sex hormone, active-vitamin-D 3 kind, and prostagladins, or two sorts or more.

[Claim 4] The medical-supplies constituent for powdered inhalation according to claim 1 which is one sort as which the excipient was chosen from a lactose, grape sugar, fruit sugar, the mannitol, the sucrose, the maltose, and the dextran, or two sorts or more.

[Claim 5] The medical-supplies constituent for powdered inhalation according to claim 1 with which the medicine particle cast by the globular form is manufactured by the spray drying method.

[Claim 6] The medical-supplies constituent for powdered inhalation according to claim 1 which has the particle diameter of the range whose 80% of the weight or more of the medicine particle cast by the globular form is 0.5 to 10 micrometer, and has the particle diameter of the range whose 95% of the weight or more of an excipient is 30 to 150 micrometer.

[Claim 7] The medical-supplies constituent for powdered inhalation according to claim 1 whose weight ratio of a medicine and an excipient is 0.1:99.9-50:50.

[Claim 8] The medical-supplies constituent for powdered inhalation according to claim 1 whose excipient is not the smooth front face of specific-surface-area $S_0 > 1.75$.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[The technical field to which invention belongs] this invention relates to the new drug constituent for powdered inhalation which the self-possessed amount in lungs of a medicine increased. Furthermore, by casting a medicine particle to a globular form in detail, the adhesion force of a medicine particle and an excipient is adjusted and it is related with the new drug constituent for powdered inhalation which the self-possessed amount in lungs of the medicine particle after being inhaled as a result increased.

[0002]

[Description of the Prior Art] The vapor is a tablet aiming at medicating the Lords, such as a trachea, a bronchial tube, and an alveolus, with a medicine from the oral cavity or a nasal cavity to a lower respiratory tract. With a lower respiratory tract here, it is defined as a trachea, a bronchial tube, a bronchiole, an alveolus, etc. among respiratory tracts.

[0003] The vapor attracts attention also as a prescribing [for the patient]-a medicine method it is put in practical use as a partial medication tablet to chest diseases, such as asthma, bronchitis, and pulmonary emphysema, and make bioactive peptide, protein, etc. shift to a whole body blood flow from an alveolus in recent years.

[0004] As a pharmaceutical form of such vapor, there are three, inhalation solution, chlorofluorocarbon or a chlorofluorocarbon-replacing material tablet, and the powder vapor. Inhalation solution is usually the solution of a medicine, it is atomized by the nebulizer, serves as a very small drop, is inhaled under a patient's spontaneous respiration, and carries out deposition in the form of a drop into a respiratory tract. Chlorofluorocarbon or a chlorofluorocarbon-replacing material tablet is a tablet in which the medicine was distributed or dissolved by chlorofluorocarbon or the chlorofluorocarbon-replacing material under pressurization, and the pressurization container called pressure-type fixed quantity nebulizer (MeteredDose Inhaler; MDI) is filled up with it, and it is used. If wide opened from MDI under pressurization, chlorofluorocarbon or a chlorofluorocarbon-replacing material will evaporate, the medicine which was being dissolved and distributed will usually serve as particle powder of a medicine, and the deposition of the time of medication will be carried out into a respiratory tract. moreover, the particle powder with which the powder vapor is mainly concerned with a medicine -- a powdered constituent -- carrying out -- an excipient etc. -- containers, such as a blister, -- being filled up -- usually -- a patient's own inhalation of air -- the particle powder in [a suitable medication machine to] this container -- powder -- aerosol -- it is-izing and inhaled and deposition is carried out into a respiratory tract as medicine powder

[0005] Among the pharmaceutical forms of these vapor, since inhalation solution has the risk of mixing, such as bacteria, in case medication with a heavy expensive and large nebulizer generally fills up a nebulizer with a ** sake and a medical fluid, it is not suitable for the patient itself prescribing a medicine for the patient except a medical institution. Although chlorofluorocarbon or a chlorofluorocarbon-replacing material tablet has lightweight MDI which is a medication machine, and portability is good, and the sealed container is filled up with a tablet and it is, chlorofluorocarbon is ozone layer depletion and a chlorofluorocarbon-replacing material is the factor of greenhouse effect, and when considering earth environment, you should refrain from the use. To these, generally, the powder vapor of the medication machine is lightweight, its portability is good, and it is constituted so that bacterial mixing may be prevented, and it is considered to be the pharmaceutical form of the ideal vapor from a component which is concerned with environmental destruction into a tablet not being included.

[0006] Furthermore, there are the following three sorts in the powder vapor.

(1) When the mixed particle with which the medicine particle and the excipient particle with a larger particle size than this medicine particle chosen from a lactose etc. were mixed uniformly is prescribed for the patient into a respiratory tract from a suitable container, although deposition is carried out to the oral cavity, the pharynx, or the pharynx, for an excipient, only a medicine particle is attainment and the powdered constituent which carries out deposition even to lower respiratory tracts, such as a trachea and a bronchial tube.

[0007] (2) The powdered constituent in which it reaches and the medicine particle which the composition medicine particle dissociated during the flight and it generated when the powdered tablet to which the granulation of the medicine particles is softly carried out, and they serve as a comparatively big particle size was prescribed for the patient into the respiratory tract from the suitable container carries out deposition to lower respiratory tracts, such as a trachea and a bronchial tube.

[0008] (3) The powdered constituent in which it will reach and this medicine particle will carry out deposition even to lower respiratory tracts, such as a trachea and a bronchial tube, if a medicine is prescribed for the patient into a respiratory tract from a suitable container by the powdered tablet which consists only of a medicine particle. Since it is difficult to divide the powdered medicine of the draft dose when there are few amounts of medicines also in these, the powdered constituent of a medicine and an excipient as shown in (1) is used in many cases.

[0009] The back excipient and medicine which were inhaled separating a powdered constituent as shown in (1), and carrying out the deposition of the excipient of a larger particle size to the oral cavity and a throat, as mentioned above, and only the medicine of a smaller particle size reaching and carrying out deposition even to a trachea, a bronchial tube, and lungs, and demonstrating the effect of a medicine on a part, or it being absorbed in blood from lungs and demonstrating systemic action is expected. However, even if medicines condensing and generating an aggregated particle with a large particle size is known and the medicine with a small particle size is inhaled, it may not reach a trachea, a bronchial tube, and lungs, but may carry out deposition to the oral cavity and a throat. Many this

phenomenon is especially accepted with a fat-soluble high medicine. Furthermore, it is known that the medicine particle with a small particle size will adhere to the excipient front face where particle size is large, if this adhesion force is too strong, it cannot dissociate from an excipient during inhalation operation, and a medicine cannot demonstrate the effect of a medicine expected by carrying out self-possessed to the oral cavity and a throat. on the other hand, if this adhesion force is too weak, a medicine adhering to a mixed container and losing in process in which a mixed-powder object is manufactured, etc. will cut In the case of an especially fat-soluble high medicine, adhesion in the mixed container of a medicine is accepted notably.

[0010]

[Problem(s) to be Solved by the Invention] The purpose of this invention sets up the adhesion force between a medicine particle and an excipient particle the optimal, and is to offer the drug constituent for powdered inhalation which made the maximum manufacture efficiency and the effect of a medicine.

[0011]

[Means for Solving the Problem] As a result of inquiring wholeheartedly, by casting a medicine particle to a globular form, this invention persons succeeded in optimizing condensation of medicine particles, and adhesion with a medicine particle and an excipient, and reached this invention.

[0012]

[Embodiments of the Invention] By this invention, a "globular form" evaluates a particle by degree-of-sphericity ψS ($=\pi x^2 / S$) of Wadell, and means 0.90 or more things. in addition -- Although x is a sphere product nominal diameter, in this invention, the volume mean diameter practically obtained by the laser diffraction type particle-size-distribution measuring device based on the principle of the Fraunhofer diffraction is used. S is the surface area of a particle and is converted from the specific surface area measured by the air permeability method or the gas transmission method. Moreover, the specific surface area S_0 (per unit weight) measured by the air permeability method or the gas transmission method with "it is smooth" says 1.75 or less thing by this invention.

[0013] In order to make the interaction between particles into the minimum, making the surface area of a particle into the minimum is a means to reach easily, if it is the contractor concerned. Therefore, it is not new to cast a medicine particle to a globular form itself. For example, in WO 96/No. 09814 specification, the claim of "the micro particle for treatment / diagnosis by the water-soluble material smooth in a globular form into which at least 90% or more has a 1 to 10-micrometer aerodynamic study-pitch diameter" is carried out. However, there is also no publication of the example which the definition of being a globular form does not have in this patent, either, and is clarified about the effect of being a globular form. The knowledge of the medicine particle cast by the globular form in the powdered vapor raising the deposition efficiency to the trachea, a bronchial tube, and lungs was done for the first time by this invention persons.

[0014] Since are and the globular form medicine particle of this invention needs the particle size for the range which is 0.5 to 10 micrometer in order to carry out self-possessed to a trachea, a bronchial tube, and lungs, by the usual granulation, it cannot be manufactured but can be manufactured by the spray drying method, the crystallization method, the supercritical fluid recrystallizing method, etc. Also in this, a spray drying method is the most common. The medicine particle of this invention by the spray drying method dissolves propionic-acid BEKUROMETAZON (it considers as Following BDP) 10g in dehydrated ethanol 500mL, and prepares a sample solution. GS-31 (YAMATO Lab Tech) is used as a spray drier. Diameter of nozzle:0.4 mm, Inlet temperature: On condition that atomizing-pressure:2.5 kg / 105-degree-C, outlet temperature:70~80 degree-C, liquid-sending speed:6.5 g/min, hot blast air-capacity:0.6 m³/min, and cm²**, spray drying of the above-mentioned sample solution can be carried out, and it can be manufactured. (Example 1 of manufacture)

Thus, the manufactured fine-particles particle is a globular form particle ($\psi S > 0.90$) looked at by the scanning-electron-microscope image which it is obtained at 50% of recovery, and is shown in drawing 1, and is a pitch diameter. They were 1.5 micrometers and the range whose 85% or more is 0.5 to 10 micrometer.

[0015] Especially although the medicine used for this invention will not be limited especially if used as inhalation in principle, what particles are easy to condense is mentioned. As such an example, a medicine with high cohesiveness is mentioned to a fat-soluble high medicine or a fat-soluble unique target. As a fat-soluble high medicine, adenocorticotropic hormone, sex hormone, active-vitamin-D 3 kind, and prostagladins are mentioned. As adenocorticotropic hormone, as sex hormone, propionic-acid BEKUROMETAZON, triamcinolone-diacetate, flunisolide, budesonide, and propionic-acid fruity KAZON etc. As active-vitamin-D 3 kind, a testosterone, estrogen, an estradiol, etc. 1alpha, 24-dihydroxy vitamin D3, 1alpha, 25-dihydroxy vitamin D3 (calciferol), KARUSHIPO triol, 1alpha-hydroxy-24-oxo vitamin D3, 1alpha, 25-dihydroxy vitamin D3 -26, 23-lactone, 1alpha, 25-dihydroxy vitamin D3 -26, 23-peroxy lactone and 26, 26, 26, 27 and 27, 27-hexafluoro - 1alpha, 25-dihydroxy vitamin D3, etc., As prostagladins, it is ***** about prostaglandin E 1 (alprostadil), prostaglandin F2alpha (dinoprost), a prostaglandin I2 (EPOPU loss tenor), BERAPUROSUTO, KURIMPUROSUTO, etc. As an example of a medicine with high cohesiveness, the amount peptides of macromolecules, such as an insulin and a calcitonin, are mentioned specifically.

[0016] Although it will not be limited especially if it is usually used as an excipient of an inhalation agent as an excipient of this invention, polysaccharide, such as a lactose, grape sugar, a mannitol, fruit sugar, a sucrose, arabinose, xylitol, a glucose, a maltose, trehaloses and these one hydrates, and a dextran, a dextrin, is mentioned, for example. Most generally [a lactose] also in these, it is used.

[0017] As long as it is the particle size which carries out deposition into the oral cavity and a throat in principle, which configuration is sufficient as the configuration of the excipient used by this invention, and it is desirable that 95% of the weight or more of particle size is the range of 30 to 150 micrometer. That is, when casting as a globular form like a medicine particle, a granulation is carried out by the method of depositing specific conditions which are indicated by the same spray drying method as a medicine particle, and the ***** No. 504427 [four to] official report etc. Moreover, when not casting to a globular form, it is prepared by the particle size of the range of desired from a big particle by the usual mechanical grinding method. However, it has a certain amount of planar structure in the front face, or an excipient is not smoother than the front face indicated by the ***** No. 504427 [four to] official report, it is porous, and the knowledge of the configuration of the rate [of self-possessed] to a trachea, a bronchial tube, and lungs where a surface area is large improving more is done by this invention persons.

[0018] The amount of medicines used by this invention changes by the strength of the effect of a medicine of a medicine, and an effective amount contains it per tablet of one batch.

[0019] The weight ratio of the medicine of this invention and an excipient is within the limits of 0.1:99.9~50:50, and this

rate changes with the amounts of medicines. Therefore, although the amount of excipients used by this invention changes with the amounts of medicines, it is within the limits of 10ng-5mg about.

[0020] The medical-supplies constituent of this invention is the BDP particle obtained by the above-mentioned example 1 of manufacture. In a V shaped rotary mixer, it can mix for 3.5 hours and 1.0g and 61.5g (following 100-400M lactose) of things which sifted out the pulverizing lactose (monohydrate-harmatose 200M; DMV company) to a 100-mesh path and 400-mesh-on can be manufactured. (Example 2 of manufacture) As a result of extracting 30 samples from the constituent obtained by doing in this way at random and measuring the BDP content, valve flow coefficient value was mostly mixed with 3.1% by homogeneity. The scanning-electron-microscope image of the manufactured constituent is shown in drawing 2.

[0021]

[Effect of the Invention] A trachea, a bronchial tube, and the medical-supplies constituent for powder inhalation with the good rate of self-possessed to lungs are offered by this invention in this way, and the meaning is high.

[0022]

[Example] Hereafter, although this invention is explained in full detail according to an example, these do not explain this invention and do not limit this invention.

[0023] [Example 1]

The inhalation efficiency evaluation this example of a propionic-acid BEKUROMETAZON globular form particle tablet carries out comparative evaluation with the following contrast tablets for the effect on inhalation delivery of the mixed-powder object (1) which comes to contain propionic-acid BEKUROMETAZON (following globular form BDP) and 100-400M lactose (specific-surface-area $S_0 > 1.75$) which were cast by the globular form obtained in the example 1 of manufacture.

- (1) Globular form BDP+100-400M lactose (this invention tablet 1)
- (2) The lactose for globular form BDP+ inhalation (this invention tablet 2)
- (3) Trituration BDP+100-400M lactose (contrast tablet 1)
- (4) The lactose for trituration BDP+ inhalation (contrast tablet 2)

It is the Pharmacopoeia of Japan BDP (Fujikawa, Inc.) in the trituration BDP here, and the lactose for inhalation (Pharmatose 325M and DMV) is the recrystallized lactose monohydrate, and it has the smooth front face ($S_0 < 1.75$). The tablets from (2) to (4) obtained BDP1.0g and the 61.5 g lactose according to the example 2 of manufacture by mixing in a V shaped rotary mixer for 3 to 4 hours. Each 30 gelatin No. 3 capsules were filled up with these [5mg] (each tablet). They are two crotches about the medication machine Inhalater MTM (BERINGA in gel HAIMU) which filled up two Anderssen cascade impactors with the above-mentioned capsule. Attracting each cascade impactor by 1CFM (=28.3 L/min) flow rate using the equipment shown in drawing 3 installed through the induction port, 30 capsules per each tablet were made to attract at intervals of 15 seconds, and it evaluated. The fixed quantity of the amount of medication machine survival, the amount of capsule survival, induction port coating weight, the pre separator of an impactor, a plate self-possessed amount, and the backup filter (BUF) self-possessed amount was carried out in the high performance chromatography about BDP for every tablet. The result of evaluation is shown in Table 1-2. In addition, this evaluation was carried out on condition that 25 degrees C and 40%RH (the same is said of the examples 2-3). The acquired value is the total value of 30 capsules, and it can be considered that a fraction (% value over the amount of encapsulation in a parenthesis) is the average of 30 capsules. 0.65-5.8 micrometers (Stage 2-6) a lower respiratory tract with as opposed to [under a tablet / clinical] a content in a fraction -- self-possessed -- a part -- it corresponds About this fraction, (1) which is this invention tablet, and (2) are equivalent, and these showed the high value (about 1.4 times) intentionally to (3) which is a contrast tablet, and (4). The tablet of (1) and (2) was more nearly intentionally [than the tablet of (3) and (4)] low about the fraction of capsule survival, and it was the result of moreover calling it (1) < (2). Moreover, in many cases, in scanning-electron-microscope observation of the fine particles for survival among a capsule, many fine particles [that the medicine particle has adhered to the lactose] and fine particles which medicine particles are condensing were especially seen by the tablet of (3) and (4) to the medicine BDP particle and the lactose having distributed and existed by the tablet of (1) and (2).

[0024]

[Table 1]

	(1) 球形 BDP+100-400M 乳糖 (本発明製剤 1) [μ g] ([%] 対充填量)	(2) 球形 BDP+吸入用乳糖 (本発明製剤 2) [μ g] ([%] 対充填量)
投与器	109.7 (4.8)	66.4 (3.7)
カプセル	368.8 (16.2)	482.7 (26.8)
インダクションポート	720.3 (31.7)	387.6 (21.5)
プレセバレーター	408.4 (18.0)	270.4 (15.0)
5.8 μ m ~ (Stage 0-1)	374.2 (16.5)	380.0 (21.1)
0.65 ~ 5.8 μ m (Stage 2-6)	289.3 (12.7)	217.8 (12.1)
~0.65 μ m (Stage 7, BUF)	4.0 (0.2)	0.0 (0.0)

[0025]

[Table 2]

(表1のつづき1)

	(3) 粉碎 BDP+100-400M 乳糖 (対照製剤1) [μg] ([%] 対充填量)	(4) 粉碎 BDP+吸入用乳糖 (対照製剤2) [μg] ([%] 対充填量)
投与器	82.4 (3.7)	177.2 (7.4)
カプセル	904.3 (40.8)	874.5 (36.4)
インダクションポート	486.6 (21.1)	350.1 (14.6)
プレセバレーター	205.8 (9.3)	424.9 (17.7)
5.8 μm~ (Stage0-1)	345.1 (15.6)	350.2 (14.6)
0.65~5.8 μm (Stage2-6)	190.3 (8.5)	227.4 (9.5)
~0.65 μm (Stage7, BUF)	2.9 (0.1)	0.0 (0.0)

[0026] [Example 2]

Spray drying of the inhalation efficiency evaluation prostaglandin E 1 (alprostadil; henceforth, PGE1) of a prostaglandin E 1 globular-form particle tablet was carried out on the same conditions as BDP, and the globular form particle (psiS> 0.9) was obtained. It is ethyl acetate about PGE1 as a contrast particle. Made it dissolve in a /heptane, it was made to recrystallize, the mortar ground the obtained crystal, and the particle of a particle size (1.9~2.0 micrometers) equivalent to a globular form particle was obtained. Like the example 1, the globular form or PGE1 ground particle, 100~400M lactose, or the lactose for inhalation was mixed with the V type mixer by the weight ratio 0.4:99.6 for 1 to 2 hours, and the following tablets were prepared.

(1) Globular form PGE1+100~400M lactose (this invention tablet 3)

(2) The lactose globular form lactose for globular form PGE1+ inhalation (this invention tablet 4)

(3) Trituration PGE1+100~400M lactose (contrast tablet 3)

(4) The lactose for trituration PGE1+ inhalation (contrast tablet 4)

It filled up 90 gelatin No. 3 capsules with 5mg of these tablets at a time like the example 1 (each tablet). Attracting each cascade impactor by 1CFM (=28.3 L/min) flow rate using the equipment shown in drawing 3 which installed the medication machine Inhalater MTM (BERINGA in gel HAIMU) filled up with the above-mentioned capsule, 90 capsules per each tablet were made to attract at intervals of 15 seconds, and it evaluated. PGE1 fixed quantity in each portion was carried out in the high performance chromatography for every tablet. The result of evaluation is shown in Table 3-4. 0.65~5.8 micrometers (Stage 2-6) (1) whose a fraction is this invention tablet, and (2) are equivalent, and these showed the high value intentionally to a contrast tablet (3) and (4). Also about the fraction of capsule survival, it was an example 1 and this inclination, the tablet of (1) and (2) was more nearly intentionally [than the tablet of (3) and (4)] low, and it was the result of moreover calling it (1) < (2).

[0027]

[Table 3]

	(1) 球形 PGE ₁ +100~400M 乳糖 (本発明製剤3) [μg] ([%] 対充填量)	(2) 球形 PGE ₁ +吸入用乳糖 (本発明製剤4) [μg] ([%] 対充填量)
投与器	47.6 (2.7)	56.6 (3.2)
カプセル	252.0 (14.3)	436.5 (24.7)
インダクションポート	558.7 (31.7)	376.4 (21.3)
プレセバレーター	315.5 (17.9)	281.0 (15.9)
5.8 μm~ (Stage0-1)	304.9 (17.3)	358.8 (20.3)
0.65~5.8 μm (Stage2-6)	275.0 (15.6)	254.5 (14.4)
~0.65 μm (Stage7, BUF)	8.8 (0.5)	3.5 (0.2)

[0028]

[Table 4]

(表3のつづき1)

	(3) 粉碎 PGE ₁ +100~400M 乳糖 (対照製剤3) [μg] ([%] 対充填量)	(4) 粉碎 PGE ₁ +吸入用乳糖 (対照製剤4) [μg] ([%] 対充填量)
投与器	57.0 (3.2)	144.4 (8.1)
カプセル	714.6 (40.1)	636.6 (35.7)
インダクションポート	365.3 (20.5)	278.2 (15.6)
プレセバレーター	172.9 (9.7)	239.0 (13.4)
5.8 μm~ (Stage0-1)	290.5 (16.3)	280.0 (15.7)
0.65~5.8 μm (Stage2-6)	181.8 (10.2)	205.1 (11.5)
~0.65 μm (Stage7, BUF)	0.0 (0.0)	0.0 (0.0)

[0029] [Example 3]

The coating weight evaluation diameter of 58mm to the stainless steel can container wall of a BDP globular form particle tablet, With the stainless steel can (one side of the base of a pillar is opened wide) of the shape of a pillar with a height of 750mm 1.5 g was taken respectively and (1) globular-form BDP+100-400M lactose (this invention tablet 1) and the lactose for (2) globular-form BDP+ inhalation (this invention tablet 2) which were manufactured in the example of manufacture and the example 1 were shaken in the base diameter direction with the shaker for 2 hours. During shake, it covered and scattering of fine particles was prevented. The free wheel plate after shake was taken and contents were taken out. Furthermore the spatula struck the stainless steel can lightly, and the powder tablet was discharged. Weighing capacity of the taken-out fine particles (it discharged) was correctly carried out with the electronic balance, and fine-particles adhesion and surface coverage were computed from the charge to a stainless steel can. Moreover, the stainless steel can was extracted in the acetonitrile of 5mL(s), the fixed quantity was carried out in the high performance chromatography, and adhesion and surface coverage were similarly computed from the charge. The value computed by the weight and extraction was equivalent, and were (1)9% and (2)16%. It was shown by the globular form lactose from this that there is [less adhesion into material] to use the usual lactose.

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]

[Drawing 1] The transmission-electron-microscope photograph of the BDP globular form particle manufactured in the example 1 of manufacture is shown.

[Drawing 2] BDP globular form particle manufactured in the example 2 of manufacture / The transmission-electron-microscope photograph of the lactose for inhalation (weight ratio 1:61.5) is shown.

[Drawing 3] The inhalation efficiency evaluation equipment used in the examples 1-2 is shown.

[Translation done.]

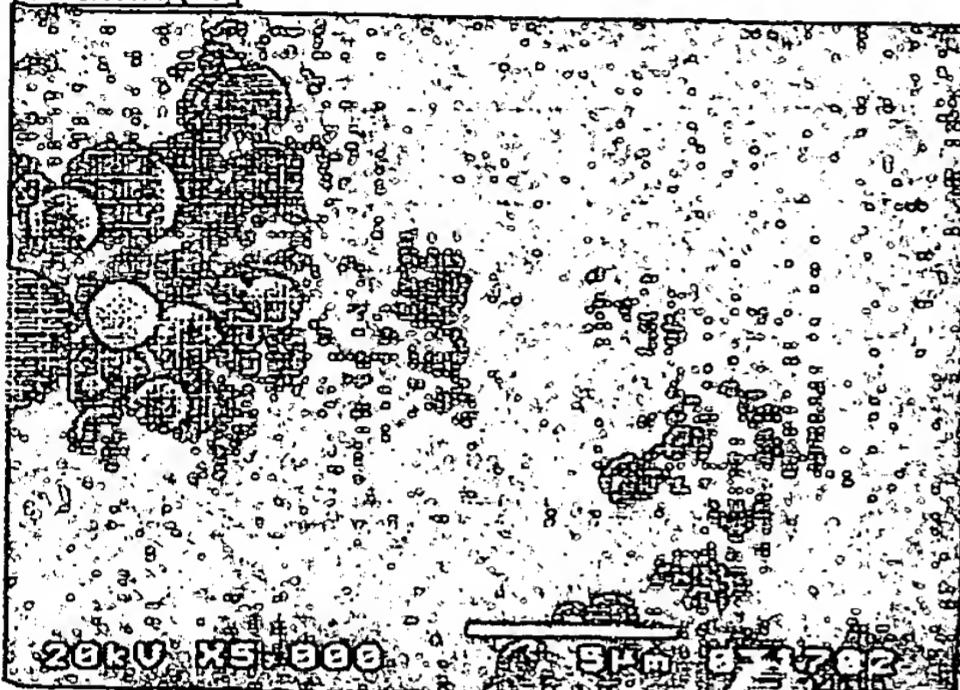
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DRAWINGS

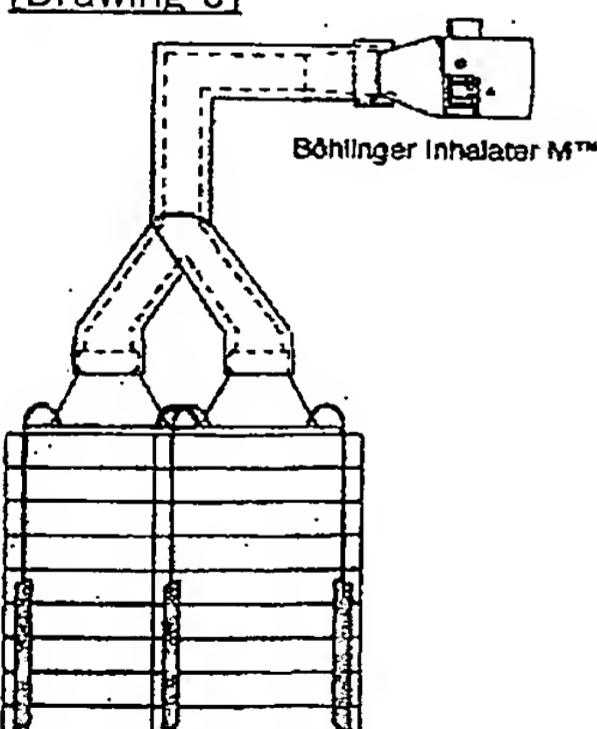
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]

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(71)出願人 000003001

帝人株式会社

大阪府大阪市中央区南本町1丁目6番7号

(72)発明者 牧野 悠治

東京都千代田区内幸町2丁目1番1号 帝人株式会社内

(72)発明者 木下 渉

東京都日野市旭が丘4丁目3番2号 帝人株式会社東京研究センター内

(74)代理人 弁理士 前田 純博

(54)【発明の名称】粉末状吸入用医薬品組成物

(57)【要約】 (修正有)

【課題】粒径の小さい薬物粒子は粒径の大きい賦形剤表面に付着することが知られており、この付着力が強すぎると薬物は吸入操作中に賦形剤から分離せず口腔、咽喉に沈着してしまい期待された薬効を発揮することができない。一方、この付着力が弱すぎると混合粉体を製造する過程で薬物が混合容器に付着してしまい損失を生じる。薬物微粒子と賦形剤粒子との間の付着力を最適に設定し、製造効率及び薬効を最大にした粉末状吸入用医薬品組成物を提供することにある。

【解決手段】球形度0.90以上に成型された薬物微粒子と賦形剤とを含んで成る粉末状吸入用医薬品組成物。

【効果】粉末状吸入剤において、薬物粒子を球形に成型することにより、その気管、気管支、肺への沈着効率を上昇させる。

【特許請求の範囲】

【請求項1】 球形度0.90以上に成型された薬物微粒子と賦形剤とを含んで成る粉末状吸入用医薬品組成物。

【請求項2】 薬物が脂溶性薬物である請求項1記載の粉末状吸入用医薬品組成物。

【請求項3】 脂溶性薬物が副腎皮質ホルモン類、性ホルモン類、活性型ビタミンD3類、プロスタグランジン類からなる群から選ばれた1種あるいは2種以上である請求項2記載の粉末状吸入用医薬品組成物。

【請求項4】 賦形剤が乳糖、ブドウ糖、果糖、マンニトール、蔗糖、麦芽糖およびデキストランから選ばれた1種あるいは2種以上である請求項1記載の粉末状吸入用医薬品組成物。

【請求項5】 球形に成型された薬物微粒子が噴霧乾燥法で製造される請求項1記載の粉末状吸入用医薬品組成物。

【請求項6】 球形に成型された薬物微粒子の80重量%以上が0.5-10 μ mの範囲の粒子径を有し、賦形剤の95重量%以上が30-150 μ mの範囲の粒子径を有する請求項1記載の粉末状吸入用医薬品組成物。

【請求項7】 薬物と賦形剤との重量比が0.1:99.9-50:50である請求項1記載の粉末状吸入用医薬品組成物。

【請求項8】 賦形剤が比表面積 $S_0 > 1.75$ の滑らかな表面でない請求項1記載の粉末状吸入用医薬品組成物。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】 本発明は薬物の肺内沈着量が増加した新規な粉末状吸入用医薬品組成物に関する。更に詳しくは薬物微粒子を球形に成型することにより薬物微粒子と賦形剤との付着力が調節され、その結果吸入された後の薬物微粒子の肺内沈着量が増加した新規な粉末状吸入用医薬品組成物に関する。

【0002】

【従来の技術】 吸入剤とは、口腔あるいは鼻腔から、気管、気管支、肺胞などの主に下気道へ薬物を投与することを目的とした製剤である。ここでいう下気道とは気道のうち、気管、気管支、細気管支、肺胞等と定義される。

【0003】 吸入剤は、喘息、気管支炎、肺気腫等の胸部疾患に対する局所投与製剤として実用化されており、また近年生理活性ペプチド類、蛋白質等を肺胞から全身血流へ移行させる投与法としても注目を集めている。

【0004】 このような吸入剤の剤型として、吸入液剤、フロンまたは代替フロン製剤、粉末吸入剤の3つがある。吸入液剤は通常薬物の水溶液であり、ネブライザーにより霧化されて微少の液滴となって患者の自発呼吸下で吸入され、気道内に液滴の形で沈着する。フロンまたは代替フロン製剤は、フロンまたは代替フロンに加圧下で薬物が分散または溶解された製剤であり、加圧式定量噴霧吸入器 (Metered Dose Inhaler; MDI) と呼ばれる

加圧容器に充填されて用いられる。投与時は、加圧下のMDIから開放されるとフロンまたは代替フロンが気化し、溶解・分散していた薬物が通常薬物の微粒子粉末となって気道内に沈着する。また、粉末吸入剤は薬物を主とする微粒子粉末を例えば粉末状組成物として賦形剤などとともにブリストー等の容器に充填し、通常患者自身の吸気により適当な投与器から該容器内の微粒子粉末が粉末エアロゾル化されて吸入され、薬物粉末として気道内に沈着する。

【0005】 これらの吸入剤の剤型のうち、吸入液剤は一般に高価で大きく重いネブライザーでの投与がのため、また薬液をネブライザーに充填する際に細菌等の混入の危険があるため、医療機関以外で患者自身が投与するには適さない。フロンまたは代替フロン製剤は、投与器であるMDIが軽量で携帯性がよく、また密封された容器に製剤が充填されているが、フロンはオゾン層破壊、代替フロンは温室効果の要因であり、地球環境を考える上ではその使用は控えられるべきである。これらに対して粉末吸入剤は、一般にその投与器は軽量で携帯性がよく、また細菌等の混入を防ぐように構成されており、製剤中に環境破壊に関わるような成分を含まないことから、理想的な吸入剤の剤型であると考えられている。

【0006】 さらに粉末吸入剤には次の3種がある。

(1) 薬物微粒子と乳糖等から選ばれる該薬物微粒子より粒径の大きい賦形剤粒子とが均一に混合された混合粒子が適当な容器から気道内に投与されると、賦形剤は口腔、咽頭あるいは喉頭に沈着するが薬物微粒子のみ気管、気管支等の下気道にまで到達、沈着する粉末状組成物。

【0007】 (2) 薬物微粒子どうしが柔らかく造粒されて比較的大きな粒径となっている粉末状製剤が、適当な容器から気道内に投与されると飛行中に構成薬物微粒子に解離され、生成した薬物微粒子が気管、気管支等の下気道に到達、沈着する粉末状組成物。

【0008】 (3) 薬物微粒子のみからなる粉末状製剤で、適当な容器から気道内に投与されると該薬物微粒子が気管、気管支等の下気道にまで到達、沈着する粉末状組成物。

これらの中でも薬物量が少ない場合は1回分投与量の粉末状薬物を分割することが困難であるために(1)のような薬物と賦形剤との粉末状組成物が使用されることが多い。

【0009】 前述したように(1)のような粉末状組成物は、吸入された後賦形剤と薬物とが分離しより大きい粒径の賦形剤は口腔、咽喉に沈着し、より小さい粒径の薬物のみが気管、気管支、肺にまで到達して沈着し局所で薬効を発揮するか、あるいは肺から血中に吸収されて全身作用を発揮することが期待されている。しかし、粒径の小さい薬物は薬物同士が凝集して粒径の大きい二次粒子を生成することが知られており、吸入されても気

管、気管支、肺に到達せず口腔、咽喉に沈着してしまうことがある。この現象は脂溶性の高い薬物で特に多く認められる。また更に、粒径の小さい薬物粒子は粒径の大きい賦形剤表面に付着することが知られており、この付着力が強すぎると薬物は吸入操作中に賦形剤から分離せず口腔、咽喉に沈着してしまい期待された薬効を発揮することができない。一方、この付着力が弱すぎると混合粉体を製造する過程で薬物が混合容器に付着してしまい損失することなどがおきる。特に脂溶性の高い薬物の場合薬物の混合容器への付着は顕著に認められる。

【0010】

【発明が解決しようとする課題】本発明の目的は、薬物微粒子と賦形剤粒子との間の付着力を最適に設定し、製造効率及び薬効を最大にした粉末状吸入用医薬品組成物を提供することにある。

【0011】

【課題を解決するための手段】本発明者らは鋭意研究した結果、薬物微粒子を球形に成型することにより薬物微粒子同士の凝集及び薬物微粒子と賦形剤との付着を最適化することに成功し本発明に到達した。

【0012】

【発明の実施の形態】本発明で「球形」とは、Wadellの球形度 $\phi_s (= \pi x_v^2 / S)$ で粒子を評価して0.90以上のものをいう。なお x_v は球体積相当径であるが、本発明では実用上フラウンホーファー回折の原理に基づくレーザー回折型粒度分布測定装置で得られる体積平均径を用いる。Sは粒子の表面積であって、空気透過法またはガス透過法により測定される比表面積から換算する。また、本発明で「滑らか」とは、空気透過法またはガス透過法により測定される比表面積 S_0 (単位重量あたり) が1.75以下のものをいう。

【0013】粒子間の相互作用を最小にするために粒子の表面積を最小にすることは当該業者であれば容易に到達する手段である。従って薬物粒子を球形に成型すること自体は新規ではない。例えば、WO96/09814号明細書において「少なくとも90%以上が1から10 μm の空力学的平均径を有する球形で滑らかな水溶性材料による治療・診断用マイクロパーティクル」がクレームされている。しかし該特許においては球形であることの定義もなく、また球形であることの効果について明らかにする実施例等の記載もない。粉末状吸入剤において球形に成型された薬物粒子がその気管、気管支、肺への沈着効率を上昇させることは本発明者らによりはじめて知見された。

【0014】本発明の球形の薬物粒子は気管、気管支、肺に沈着するためにその粒径が0.5-10 μm の範囲にある必要から通常の造粒では製造できず、噴霧乾燥法、晶析法、超臨界流体再結晶化法などで製造することができる。この中でも噴霧乾燥法がもっとも一般的である。噴霧乾燥法による本発明の薬物微粒子は、プロピオノ酸ベクロメタゾン (以下BDPとする) 10 gを無水エタノール5

00mLに溶解してサンプル溶液を調製し、噴霧乾燥機としてCS-31 (ヤマトラボテック(株)) を用い、ノズル径: 0.4 mm、入口温度: 105°C、出口温度: 70-80°C、送液速度: 6.5 g/min、熱風風量: 0.6 m³/min、噴霧圧力: 2.5 kg/cm²、の条件で上記サンプル溶液を噴霧乾燥して製造することが出来る。(製造例1)

このようにして製造された粉体粒子は回収率50%で得られ、図1に示す走査型電子顕微鏡像に見られる球形粒子 ($\phi_s > 0.90$) であり、平均径 1.5 μm 85%以上が0.5-10 μm の範囲であった。

【0015】本発明に用いられる薬物は原則としては吸入薬として使用されるものであれば特に限定されないが、特に粒子同士が凝集しやすいものが挙げられる。そのような例としては脂溶性の高い薬物、あるいは特異的に凝集性が高い薬物が挙げられる。脂溶性の高い薬物としては副腎皮質ホルモン類、性ホルモン類、活性型ビタミンD₃類、プロスタグラジン類などが挙げられる。副腎皮質ホルモン類としては、プロピオノ酸ベクロメタゾン、酢酸トリアムシノロン、フルニソリド、ブデソニドおよびプロピオノ酸フルチカゾンなど、性ホルモン類としては、テストステロン、エストロジエンおよびエストラジオールなど、活性型ビタミンD₃類としては、1 α 、2 α -ジヒドロキシビタミンD₃、1 α 、25-ジヒドロキシビタミンD₃ (カルシフェロール)、カルシポトリオール、1 α -ヒドロキシ-24-オキソビタミンD₃、1 α 、25-ジヒドロキシビタミンD₃-26,23-ラクトン、1 α 、25-ジヒドロキシビタミンD₃-26,23-パーオキシラクトンおよび26,26,26,27,27,27-ヘキサフルオロ-1 α 、25-ジヒドロキシビタミンD₃など、プロスタグラジン類としては、プロスタグラジンE₁ (アルプロスタジル)、プロスタグラジンE₂ (ジノプロスト)、プロスタグラジンI₂ (エボプロステノール)、ベラプロストおよびクリンプロストなどを挙げられる。特異的に凝集性が高い薬物の例としてはインスリン、カルシトニンなどの高分子量ペプチド類が挙げられる。

【0016】本発明の賦形剤としては通常吸入剤の賦形剤として使用されるものであれば特に限定されないが、例えば乳糖、ブドウ糖、マンニトール、果糖、蔗糖、アラビノース、キシリトール、デキストロース、麦芽糖およびトレハロースおよびこれらの1水和物や、デキストラン、デキストリン等多糖類が挙げられる。これらの中でも乳糖が最も一般的に使用される。

【0017】本発明で使用される賦形剤の形状は原則としては口腔、咽喉内に沈着するような粒径であればいずれの形状でもよく、95重量%以上の粒径が、30-150 μm の範囲であることが好ましい。つまり、薬物微粒子と同様に球形として成型する場合には薬物微粒子と同様な噴霧乾燥法や特表平4-504427号公報に記載されているような特定の条件での析出法などで造粒される。また、球形に成型しない場合には通常の機械的粉碎法で大

きな粒子から所望の範囲の粒径に調製される。しかし、賦形剤が特表平4-504427号公報に記載された表面よりも滑らかでなく、表面にある程度の平面構造を持っていたり、あるいは多孔状で表面積が大きい形状の方がより気管、気管支、肺への沈着率が向上することが本発明者らにより知見されている。

【0018】本発明で使用される薬物量は薬物の薬効の強さにより変わり、1回分の製剤単位に有効な量が含有される。

【0019】本発明の薬物と賦形剤との重量比は0.1:9.9-50:50の範囲内であり、この割合は薬物量によって変化する。従って本発明で使用される賦形剤量は薬物量により変化するが、およそ10ng-5mgの範囲内である。

【0020】本発明の医薬品組成物は、上記の製造例1により得たBDP微粒子1.0g、および微粉碎乳糖（一水和物；Pharmatose 200M DM社）を100メッシュパス、400メッシュオンに篩い分けたもの（以下100-400M乳糖）61.5gを、V型混合機にて3.5時間混合して製造することが出来る。（製造例2）このようにして得られた組成物から無作為に30サンプルを抽出してそのBDP含量を測定した結果、CV値が3.1%とほぼ均一に混合されていた。製造された組成物の走査型電子顕微鏡像を図2に示す。

【0021】

【発明の効果】かくして本発明により気管、気管支、肺への沈着率が良好な粉末吸入用医薬品組成物が提供され、その意義は高い。

【0022】

【実施例】以下、実施例により本発明を詳述するが、これらは本発明を説明するものであって本発明を限定するものではない。

【0023】 [実施例1]

プロピオン酸ベクロメタゾン球形微粒子製剤の吸入効率評価

本実施例は、製造例1にて得られた球形に成型されたプロピオン酸ベクロメタゾン（以下球形BDP）と100-400M乳糖（比表面積 $S_0 > 1.75$ ）を含んでなる混合粉体（1）の吸入送達上の効果を、以下の対照製剤との比較評価を実施したものである。

(1) 球形BDP+100-400M乳糖（本発明製剤1）

(2) 球形BDP+吸入用乳糖（本発明製剤2）

(3) 粉碎BDP+100-400M乳糖（対照製剤1）

(4) 粉碎BDP+吸入用乳糖（対照製剤2）

ここでいう粉碎BDPとは日本薬局方BDP（藤川（株））であり、また吸入用乳糖（Pharmatose 325M DM社）とは再結晶された乳糖一水和物であって、滑らかな表面（ $S_0 < 1.75$ ）を有している。（2）から（4）までの製剤は、製造例2に準じてBDP1.0gと乳糖61.5gをV型混合機にて3-4時間混合することにより得た。これらをゼラチン3号カプセル（各製剤について）30個に、5mgずつ充填した。アンダーセンカスケードインパクター2台に、上記カプセルを充填した投与器Inhalater MM（ベーリンガー・インゲルハイム社）を2股のインダクションポートを介して据え付けた図3に示す装置を用いて、それぞれのカスケードインパクターを1CFM（=28.3L/min）流量で吸引しながら、15秒間隔で各製剤あたり30個のカプセルを吸引させ評価した。各製剤ごとに、BDPについて、投与器残存量、カプセル残存量、インダクションポート付着量、インパクターのプレセバレーター、プレート沈着量、バックアップフィルター（BUF）沈着量を高速液体クロマトグラフィーにて定量した。評価の結果を表1・2に示す。なおこの評価は25°C、40%RHの条件で実施した（実施例2～3も同じ）。得られた値は30カプセルの合計値であり、フラクション（括弧内のカプセル充填量に対する%値）は30カプセルの平均値とみなすことができる。0.65～5.8μm（Stage2-6）のフラクションは、製剤中含量に対する臨床における下気道沈着分に相当する。このフラクションについては本発明製剤である

(1) および(2)は同等であり、これらは対照製剤である(3)および(4)に対して有意に高い値（約1.4倍）を示した。カプセル残存のフラクションについて

(1) および(2)の製剤は、(3) および(4)の製剤より有意に低く、しかも(1) < (2)という結果であった。また、特にカプセル中残存分の粉体の走査型電子顕微鏡観察において、(1)と(2)の製剤では多くの場合、薬物BDP微粒子と乳糖とが分散して存在していたのに対して、(3)および(4)の製剤では薬物微粒子が乳糖に付着したままの粉体、および薬物微粒子同士が凝集している粉体が多くみられた。

【0024】

【表1】

	(1) 球形BDP+100-400M乳糖 (本発明製剤1) [μg] ([%] 対充填量)	(2) 球形BDP+吸入用乳糖 (本発明製剤2) [μg] ([%] 対充填量)
投与器	109.7 (4.8)	66.4 (3.7)
カプセル	368.8 (16.2)	482.7 (26.8)
インダクションポート	720.3 (31.7)	387.6 (21.5)
プレセバレーター	408.4 (18.0)	270.4 (15.0)
5.8 μm~ (Stage0-1)	374.2 (16.5)	380.0 (21.1)
0.65~5.8 μm (Stage2-6)	289.3 (12.7)	217.8 (12.1)
~0.65 μm (Stage7, BUF)	4.0 (0.2)	0.0 (0.0)

【0025】

【表2】

(表1のつづき1)

	(3) 粉碎BDP+100-400M乳糖 (対照製剤1) [μg] ([%] 対充填量)	(4) 粉碎BDP+吸入用乳糖 (対照製剤2) [μg] ([%] 対充填量)
投与器	82.4 (3.7)	177.2 (7.4)
カプセル	904.3 (40.8)	874.5 (36.4)
インダクションポート	486.6 (21.1)	350.1 (14.6)
プレセバレーター	205.8 (9.3)	424.9 (17.7)
5.8 μm~ (Stage0-1)	345.1 (15.6)	350.2 (14.6)
0.65~5.8 μm (Stage2-6)	190.3 (8.6)	227.4 (9.5)
~0.65 μm (Stage7, BUF)	2.9 (0.1)	0.0 (0.0)

【0026】 [実施例2]

プロスタグランジンE₁ 球形微粒子製剤の吸入効率評価
プロスタグランジンE₁ (アルプロスタジル；以下PGE₁)
をBDPと同じ条件で噴霧乾燥し、球形粒子 ($\psi_s > 0.9$)
を得た。対照粒子としてPGE₁を酢酸エチル/ヘブタンに
溶解させて再結晶させ、得られた結晶を乳鉢で粉碎して
球形粒子と同等の粒径 (1.9~2.0 μm) の粒子を得た。
実施例1と同様に、球形または粉碎したPGE₁粒子と100-
400M乳糖または吸入用乳糖を、重量比0.4:99.6でV型混
合器にて1-2時間混合し、以下の製剤を調製した。

- (1) 球形PGE₁ + 100-400M乳糖 (本発明製剤3)
- (2) 球形PGE₁ + 吸入用乳糖球形乳糖 (本発明製剤4)
- (3) 粉碎PGE₁ + 100-400M乳糖 (対照製剤3)
- (4) 粉碎PGE₁ + 吸入用乳糖 (対照製剤4)

実施例1と同様に、これら製剤をゼラチン3号カプセル
(各製剤について) 90個に、5mgずつ充填した。上記カ

プセルを充填した投与器Inhalater MM (ベーリング
・インゲルハイム社) を据え付けた図3に示す装置を用
いて、それぞれのカスケードインパクターを1CFM (=28.
3L/min) 流量で吸引しながら、15秒間隔で各製剤あたり
90個のカプセルを吸引させ評価した。各製剤ごとに、各
部分でのPGE₁定量を高速液体クロマトグラフィーにて実
施した。評価の結果を表3・4に示す。0.65~5.8 μm
(Stage2-6)のフラクションは本発明製剤である(1)お
よび(2)は同等であり、これらは対照製剤(3)および(4)
に対して有意に高い値を示した。カプセル残存
のフラクションについても実施例1と同傾向であり、
(1)および(2)の製剤は(3)および(4)の製剤
より有意に低く、しかも(1) < (2)という結果であ
った。

【0027】

【表3】

	(1) 球形PGE ₁ +100-400M乳糖 (本発明製剤3) [μg] ([%] 対充填量)	(2) 球形PGE ₁ +吸入用乳糖 (本発明製剤4) [μg] ([%] 対充填量)
投与器	47.6 (2.7)	56.6 (3.2)
カプセル	252.0 (14.3)	436.5 (24.7)
インダクションポート	558.7 (31.7)	376.4 (21.3)
プレセバレーター	315.5 (17.9)	281.0 (15.9)
5.8 μm~ (Stage0-1)	304.9 (17.3)	358.8 (20.3)
0.65~5.8 μm (Stage2-6)	275.0 (15.6)	254.5 (14.4)
~0.65 μm (Stage7, BUF)	8.8 (0.5)	3.5 (0.2)

【0028】

【表4】

(表3のつづき1)

	(3) 粉碎PGE ₁ +100-400M乳糖 (対照製剤3) [μg] ([%]対充填量)	(4) 粉碎PGE ₁ +吸入用乳糖 (対照製剤4) [μg] ([%]対充填量)
投与器	57.0 (3.2)	144.4 (8.1)
カプセル	714.6 (40.1)	636.6 (35.7)
インダクションポート	365.3 (20.5)	278.2 (15.6)
プレセバレーター	172.9 (9.7)	239.0 (13.4)
5.8 μm～ (Stage0-1)	290.5 (16.3)	280.0 (15.7)
0.65～5.8 μm (Stage2-6)	181.8 (10.2)	205.1 (11.5)
～0.65 μm (Stage7, BUP)	0.0 (0.0)	0.0 (0.0)

【0029】 [実施例3]

BDP球形微粒子製剤のステンレス缶器壁への付着量評価
直径58mm、高さ750mmの円柱状のステンレス缶（円柱の底面の一方は開放されている）に、製造例および実施例1で製造した、（1）球形BDP+100-400M乳糖（本発明製剤1）、（2）球形BDP+吸入用乳糖（本発明製剤2）を各々1.5gをとり、2時間振盪機によって底面直径方向に振盪した。振盪中はフタをして粉体の飛散を防いだ。振盪後フタをとり、内容物を取り出した。さらにステンレス缶をスパーテルで軽くたたくなどして粉末製剤を排出した。取り出した（排出した）粉体を電子天秤にて正確に秤量して、ステンレス缶への仕込み量から粉体付着・吸着率を算出した。またステンレス缶を5mLの

アセトニトリルにて抽出して高速液体クロマトグラフィーにて定量し、同様に仕込み量から付着・吸着率を算出した。重量および抽出により算出した値は同等であり、（1）9%（2）16%であった。これより球形乳糖より通常の乳糖を用いたほうが、材料への付着が少ないことが示された。

【図面の簡単な説明】

【図1】 製造例1で製造したBDP球形微粒子の透過型電子顕微鏡写真を示す。

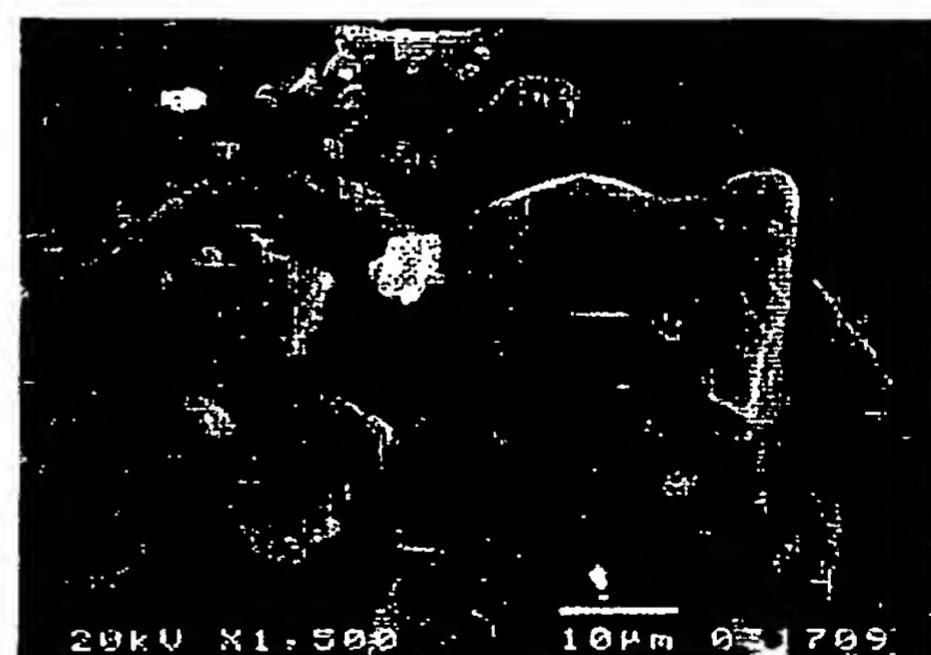
【図2】 製造例2で製造したBDP球形微粒子 / 吸入用乳糖（重量比 1:61.5）の透過型電子顕微鏡写真を示す。

【図3】 実施例1～2で用いた吸入効率評価装置を示す。

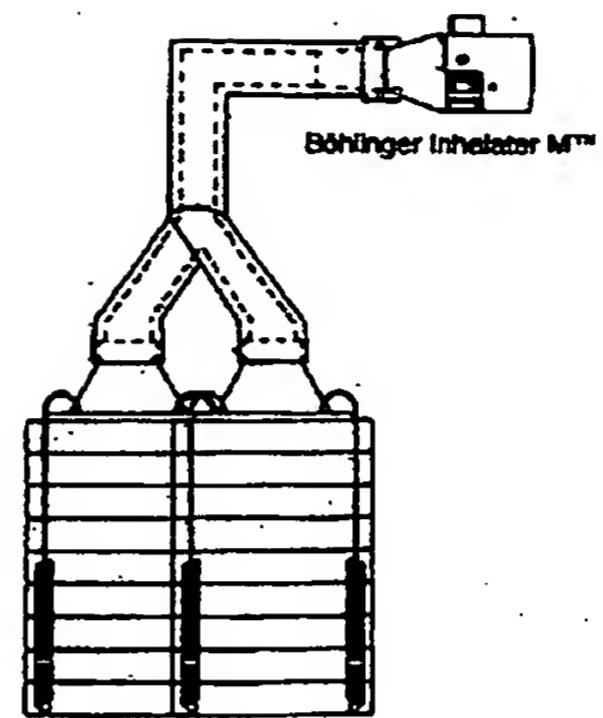
【図1】



【図2】



【図3】



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